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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,762	09/05/2003	Charles R. Cantor	701586-053023	6905

50607 7590 05/11/2009

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
05/11/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/655,762	CANTOR ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 10-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 10-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on February 10, 2009.

Preliminary Remark

Claims 4-9 and 14 are canceled.

Claims 1-3 and 10-13 are pending and are under prosecution herein.

Claim Rejections - 35 USC § 103

The rejection of claims 1-3 and 10-13 under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (Nucleic Acids Research, 1989, vol. 17, no. 22, pages 9437-9446; IDS ref) in view of Amexis et al. (PNAS, October 2001, vol. 98, no. 21, pages 12097-12102) and Ross et al. (BioTechniques, September 2000, vol. 29, pages 620-629)[1], made in the Office Action mailed on August 11, 2008 is maintained for the reasons already of record.

Applicants' arguments presented in the Amendment received on February 10, 2009 have been fully considered but they are not deemed persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

Becker et al. disclose a method of measuring the amount of target nucleic acid sequence in a biological sample, comprising the steps:

a) preparing a sample by adding known amount of a standard nucleic acid, wherein said standard nucleic acid has a single nucleotide sequence difference from the target nucleic acid (page

[1] This rejection was already made in the Final Rejection mailed on November 21, 2007, wherein Ross et al. reference was cited as an evidentiary reference for Official Notice taken. The Final Rejection under this practice was justified as set forth in MPEP 2144.03(D). The Ross reference is now being cited as a part of the references being relied upon in the present rejection.

9437, bottom paragraph, in the phrase, "mutated cDNA serves as internal standard"; and page 9438, 2nd paragraph; Figure 1);

b) amplifying the sample of step (a) (see Figure 1, via PCR);

c) using a further method to enhance the difference between the standard and the target nucleic acid sequence at the site resulting in enhanced products so that the difference created by the at least one base between the standard and the target nucleic acid can be detected (the digestion step of Figure 1 which enhances the difference between the standard and the target nucleic acid);

d) quantifying the enhanced products of step (c) by measuring the ratio of the amplified target nucleic acid to the amplified standard nucleic acid to measure the amount of target nucleic acid present in the sample (Figure 2; page 9442, bottom paragraph).

The target nucleic acid is mRNA (page 9437, 2nd paragraph).

The enhancement is achieved via an enzyme which specifically cleaves at the site of differentiation (*Eco*RI digesion; page 9442, bottom paragraph).

Becker et al. do not employ mass spectrometry in their quantification method (claims 4 and 8).

Becker et al. do not explicitly disclose a method of performing primer extension at the site of differentiation (claim 5), or allele-specific hybridization at the site of differentiation (claim 7).

Becker et al. do not explicitly disclose that the method measures the amount of at least 5, 10, 25, or 50 target nucleic acid sequences using at least 5, 10, 25, or 50 standard nucleic acids, respectively (claims 10-13).

Amexis et al. disclose a method of quantifying a target nucleic acid in a sample, in particular, RNA virus (thus infectious agent), wherein the method comprises the steps of:

a) amplification of a target nucleic acid with a pair of primers (Figure 1B; page 12098, 2nd column, 3rd paragraph);

b) amplifying the amplified product with MassExtend primers which is specific for a point mutation (Figure 1B; page 12098, 2nd column, 3rd paragraph (middle)); and

c) detecting and quantifying the amplified products (Figure 1B; page 12098, 2nd column, 3rd paragraph (bottom); Abstract; page 12098, 1st column, 3rd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Becker et al. and with the teachings of Amexis et al., thereby arriving at the claimed invention for the following reasons.

The method employed by Becker et al., which is drawn to the amplifying the target nucleic acid and the standard nucleic acid (which contains a single nucleotide mutation) via use of primers which flank the target nucleic acid region, employs more than a decade old technique – that is – restriction digest, electorphoresis, followed by the radiolabeled (^{32}P) quantitation method.

Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to employ a non-radioactive method of accurately quantitating the target nucleic acid, such as MALDI-TOF, thereby arriving at the claimed invention.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at combining the teachings since methods of quantification employing mass spectrometry, such as SNuPE (single nucleotide primer extension), have been well-established.

For example, multiplex detection of different target nucleic acids (i.e., different markers) via MALDI-TOF was known prior to Applicants' filing of the application.

> "A main advantage of MALDI-TOF MS-based genotyping is its ability to multiplex many primer extension assays within a single sample…Multiplex PCR and primer extension assays were performed for the CP450 polymorphism and a polymorphism in human LDLR region by amplifying homozygote and heterozygote samples. Multiplex PCR products from heterozygous mutant and homozygote samples were combined … and the mixture was genotyped. The data show unambiguous detection of the low-abundance alleles for both loci tested. A quantitation study was not performed for the multiplex experiments; however, the data are presented here to provide a basis for future investigation." (page 625, Ross et al., "Quantitative Approach to Single-Nucleotide Polymorphism Analysis Using MALDI-TOF Mass Spectrometry," BioTechniques, September 2000, vol. 29, pages 620-629)

Given the fact that Amexis et al. amplify a known target nucleic acid sequence via use of a flanking primer pairs, followed by the mutation-specific primer extension, one of ordinary skill in the art would have recognized that the amplification products of Becker et al., would have served equally well for the mutation-specific primer extension, which would have been necessary for the subsequent mass spectrometric analysis.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants traverse the rejection.

Applicants state that the amendment taken to claims make "explicit that which was implicit, namely that the present method is directed to quantification of the amount, not relative quantification and that the quantification is performed using a single base extension reaction." (page 4, Response).

It is respectfully submitted that a generic recitation of the term, "quantification" necessarily includes both "absolute" and "relative" quantification. Therefore, it is respectfully submitted that Applicants' statement that a generic recitation of the term, "quantifying" the enhanced products implicitly only embodies an absolute quantification is simply erroneous. For example, U.S. Patent No. 7,291,699 states:

> "The term, 'quantifying' or 'quantitating' when used in the context of quantifying transcription levels of a gene can refer to absolute or relative quantification." (column 46, lines 3-6)

Clearly, a generic recitation of term, "quantifying" or "quantiation" does not limit its scope to only an absolute quantification.

Next, Applicants state that the present Examiner ignores Ross as a whole and the Declaration by Dr. Ding submitted in the amendment dated September 10, 2007 (page 4, bottom paragraph, Response). Applicants reference to Dr. Ding's statement regarding problems known to skilled artisans when using MALDI-TOF MS and why a skilled artisans would not have expected the claimed method to work (page 4, bottom paragraph, Response).

It is respectfully submitted that Dr. Ding's declaration does not produce any "problems known to a skilled artisan" which would have led a skilled artisan that the claimed method "would not have" work.

The substance of Dr. Ding's declaration reviewed and it is respectfully pointed out that the only so-called "problem" identified by Dr. Ding (as pointed out by Applicants) is in that MassArray is very sensitive which may also detect artifacts found in detection mixtures (13th statement of the declaration). While one may agree that such is problematic, Applicants' assertion that this problem would led a skilled artisan to believe that quantification using MassArray would have been problematic and thus (would not have worked), is overreaching and erroneous.

Amexis and Ross clearly demonstrate quite plainly, that quantification using Mass spectormetry achievable:

> "The inherent high molecular weight resolution of MALDI-TOF MS conveys high specificity and good signal-to-noise ratio for performing accurate quantitation. The method described maximize the sensitivity and quantitative capacity of MALDI-TOF MS while preserving the throughput and economic advantages of the MALDI-TOF platform. Using

the format described, we demonstrate that allele frequencies as low as 5% can be detected quantitatively and unambiguously." (Abstract, Ross et al.)

Although, as pointed out by Applicants, Ross et al. do disclose some problems associated with quantifying an allele in the presence of an excess of another, typically in the alleles differing by 16 Da or less which may not be observed and that the area measurement of a low-intensity extension product within 40 Da of another allele may be confounded.

However, Ross et al. disclose that they can circumvent this problem by using a modified protocol, which adds a dye to one of chain-terminating nucleotides, so as to increase the mass difference (see Figure 1B).

Clearly, while some known problems may exist, the art also provides a way to overcome such problem, which would prove to a skilled artisan that the use of MALDI-TOF for quantitation is achievable.

In addition, Applicants appear to distinguish between Ross's method over the instantly claimed invention based on the usage of the term, "modified base extension reaction." (page 5, 2nd paragraph).

This argument is also not found persuasive because the instant claim only requires that the single-base primer extension is performed and one of the solutions which Ross uses only provides a single-base primer extension. The fact that this is described as a "modified" method does not in anyway distinguish the claimed invention from that disclosed by Ross.

The only merit to Applicants' argument over the prior art of record is in that Amexis is drawn to a relative quantitation (i.e., measurement of one nucleic acid in relation to another nucleic acid). The disclosure of Ross is not as explicit in that the artisans do not express whether the quantitation is a relative one or absolute.

However, based on the teaching provided for by Becker et al., it is deemed that one of ordinary skill in the art would have had a reasonable expectation of success at combining the teachings of the artisans, thereby arriving at the claimed invention.

Becker et al. employ a method of absolute quantitation of a nucleic acid, wherein the artisans co amplify a target nucleic acid with a standard, which contains the identical nucleic acid sequence with that of the target, except for a single nucleotide.

Since known varying amounts (serial dilutions) of standards are amplified (i.e,. spiked in to the amplification reaction), along with the target nucleic acid, allowing one to quantitate the amount of the target nucleic acid present in a sample:

> "The concept is as follows. RNA transcribed *in vitro* from the mutated cDNA serves as internal standard. In principle, PATYY resembles a titration system. Identical portions of total RNA are 'spiked' with decreasing known amounts of internal standard RNA. After conversion to cDNA and polymerase chain reaction (PCR), the amplified DNA fragments are digested with the appropriate restriction endonuclease to discriminate between DNA derived from endogenous target mRNA and DNA derived from exogenous, mutated standard RNA. In a dilution series with internal standard, the samples contain progressively more 'endogenous' DNA fragments (not cutable) and fewer 'exogenous' DNA fragments (cutable). Only one sample will contain equal or nearly equal amounts of both types of DNA, reflecting equal starting amounts of the corresponding RNA species. The known amount of *in vitro* transcript added to this sample is identical to the amount of mRNA to be analysed." (page 9437, bottom paragraph to page 9438, 1st paragraph).

This is precisely what Applicants do in their quantification:

> "In this experiment, two DNAs differ only by one nucleotide are mixed at different ratios (10:1, 3:1, 1:1, 1:3, 1:10) with a constant total concentration of $2*10^7$ ug/uL....Figure 4 shows the mass spectrum from template mixture of five different ratios. Figure 5 shows the correlations between peak area ratios in mass spectrum and DNA template ratios pre-determined for analysis." (section [0049])

While Becker et al. establishes a standard curve based on their gel run and hybridization (i.e., intensity of the hybridized probes), the instant invention generates the standard curve based on the mass analysis. The question to be asked is whether one of ordinary skill in the art at the time the

invention was made would have been motivated to combine the teachings of Becker, which uses outdated gel-run separation, followed by blotting and hybridization, or more sensitive system such as MALDI-TOF which produces, "accurate quantitation" (from Ross et al.)

The absolute quantitation is based on the comparing the amount of signal determined from the target nucleic acid against the amount of signal determined from known varying amounts of standard nucleic acids (i.e., standard curve) and since the MALDI-TOF assay produced consistent and reliable quantitation of signals, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at combining the teachings of the references, thereby arriving at the invention as claimed.

With regard to the employing the area under the peak of the spectrometry read out, such technique has been commonly employed, as shown by Ross et al. (see page 623, 2nd column).

Therefore, the invention as claimed is deemed *prima facie* obvious over the cited references.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 and 10-13 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/589,709. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are conflicting in the subject matter in that both inventions employ the use of a standard (or competitor) which has a different sequence that the sequence of the target nucleic acid for the purpose of quantifying, wherein the application clearly contemplates mass spectrometry.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants state that a Terminal Disclaimer will be filed (claim 5, bottom paragraph, Response).

As no terminal disclaimer has been filed to date and the '709 is the senior party, the provisional double patenting rejection is maintained herein.

MPEP 804(I)(B)(1) is clear in that a terminal disclaimer must be required for a later-filed prior to its issuance.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is

on flex-time schedule and can best be reached from 9:00 a.m. to 5:30 p.m (M-F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
Primary Examiner
Art Unit 1637
5/11/2009

/YJK/